

Are Blastogenetic Anomalies Sporadic?

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Opitz [Birth Defects, 1993, 1:3–37] postulated that sporadic defects of blastogenesis generally are highly lethal and have a low recurrence risk. We have observed that mothers of infants with blastogenetic defects have more previous abortions than mothers of children with nonblastogenetic defects or than mothers of control infants. Thus the high lethality of blastogenetic abnormalities may be responsible for the spontaneous abortions, and there may be a potential for an increased recurrence risk in some cases. Our results also show that the increased rate of spontaneous abortions is not similar for all blastogenetic defects, since it is not elevated in mothers of infants with neural tube defects (NTD). Further, our analysis does not confirm the relationship between spontaneous abortions in the preceding pregnancy and the occurrence of NTD previously reported by other authors. *Am. J. Med. Genet.* 68:381–385, 1997.

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INTRODUCTION

Opitz [1993] stated that some defects of blastogenesis, particularly associations, are highly lethal, show no altered sex ratio, have low recurrence risk, include a high proportion of twins, and overwhelmingly affect the midline. Here we present an analysis of previous abortions in mothers of infants with and without blastogenetic defects as well as in a control group of nonmalformed infants.

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MATERIALS AND METHODS

The study was based on liveborn malformed infants identified by the Spanish Collaborative Study of Congenital Malformations (EC EMC). This is a hospital-based case-control study and surveillance system. Children are examined during the first 3 days of life to identify major and/or minor defects. For each case, the next nonmalformed infant of the same sex born in the same hospital is selected as a control subject. Once the case and control infants have been identified, the same physicians interview the mothers of both to gather information on family history, prenatal exposures, and obstetrical data. This encompasses a systematic recording of all previous pregnancies, including those that, according to the mother's information, ended in spontaneous abortion. Detailed descriptions of the EC EMC methodology have been published elsewhere [Martínez-Frías et al., 1991; Martínez-Frías and Urioste, 1994; Martínez-Frías, 1994, 1995].

Between April 1976 and June 1993, the EC EMC surveilled a total of 1,074,029 liveborn infants. Among these, 20,891 were selected as cases, because they had major and/or mild defects and some minor anomalies detected during the first 3 days of life, and 20,524 as controls. The mothers of 20,689 (99.03%) cases and 20,389 (99.34%) controls had specified data on the outcome of previous pregnancies. Our study group comprises the 12,224 mothers of cases and 12,018 mothers of control infants who had two or more pregnancies.

As described previously [Martínez-Frías, 1995; Martínez-Frías et al., 1995], the EC EMC data base is structured using a relational data base that can be expanded by adding information through a table related to the existing ones by any of their fields. Using this capability, we have established a table including 171 codes for blastogenetic defects. We have considered as blastogenetic malformations all those defects that are presumably produced or induced during the first four weeks of gestation (Table I).

RESULTS

The proportion of mothers who had at least one previous spontaneous abortion was 26.24% among those having children with blastogenetic defects, 24.85% in those of children with nonblastogenetic defects, and 21.99% in the mothers of normal control infants (Table II). The differences are statistically highly significant ($P = 0.000002$) due to the lower proportion observed in

TABLE I. Blastogenetic Defects Included in Present Study

Conjoined twins	Esophageal duplication
Acardia-acephalus twinning	Agenesis of the stomach
Otocephaly	Intestinal duplication
Atelencephaly-aprosencephaly	Agenesis of the gallbladder
Anencephaly	Accessory gallbladder
Encephalocele	Renal agenesis
Spina bifida	Agenesis of the adrenal glands
Holoprosencephaly	Bladder duplication
Anophthalmia	Exstrophy of bladder
Anotia	Exstrophy of cloaca
Amelia	Anal atresia
Anomalies of the body stalk/wall	Sirenomelia
Limb-body wall complexes	Caudal regression
Ectopia cordis	Sacroccygeal teratoma
Pentalogy of Cantrell	Acrorenal field defect
Conotruncal septation defects	Polyasplenia field defect
DiGeorge sequence	Situs inversus
Diaphragmatic defects	Axial mesodermal dysplasia complex
Tracheal agenesis	Vertebral segmentation anomalies
Lung agenesis	Spondylocostal/thoracic dysostosis
Tracheoesophageal fistula	

the control group. When we separate the mothers into those who had only two pregnancies and those who had three or more pregnancies, the differences are statistically significant only in mothers with two pregnancies ($P = 0.001$), also due to a lower proportion of previous spontaneous abortions in mothers of control infants. The proportion of mothers with any number of previous abortions in those with three or more pregnancies approximates 40% in all three groups ($P = 0.32$).

Table III analyzes the proportion of pregnancies ending in spontaneous abortion among the total number of pregnancies in the three study groups. The proportion of pregnancies ending in spontaneous abortions was 11.41% in mothers of infants with blastogenetic defects, 10.55% in mothers of infants with nonblastogenetic defects, and 9.56% in mothers of control infants ($P = 0.00001$). These significant results reflect the differences of the two groups of mothers of malformed infants with the mothers of control infants. When the mothers are separated by number of pregnancies, the differences are statistically significant only in the mothers with two pregnancies, suggesting that in malformed infants the proportion of abortions in the preceding pregnancy is higher than in controls.

Table IV compares the number of pregnancies resulting in spontaneous abortions in mothers of children with neural tube defects (NTD), mothers of children with blastogenetic abnormalities other than NTD, and

mothers of children with nonblastogenetic defects. The table shows that only the proportions of spontaneous abortions in mothers with three or more pregnancies are significantly different ($P = 0.054$). This is due to the statistically significant difference ($P = 0.02$) observed between infants with blastogenetic defects other than NTD (14.85%) and infants with nonblastogenetic defects (12.86%). Table IV also shows that the proportion of previous abortions among mothers with only two pregnancies is higher in mothers of infants with NTD, although the differences do not reach the level of significance.

To analyze further the possible effect of having an abortion in the preceding pregnancy, we studied the proportion of mothers who had a spontaneous abortion in the pregnancy preceding the birth of an infant with blastogenetic defects, an infant with nonblastogenetic defects, and a normal control (Table V). The differences are statistically very significant ($P = 0.00002$), due to a higher proportion of preceding spontaneous abortions in mothers of malformed infants whether with blastogenetic or nonblastogenetic defects than in control infants.

Table VI shows a similar comparison among mothers of infants with NTD, with blastogenetic defects other than NTD, and with nonblastogenetic defects. The differences are not statistically significant ($P = 0.26$), although the percentage of spontaneous abortions in the

TABLE II. Number and Proportion of Mothers With Previous Spontaneous Abortions in Each Study Group

	Blastogenetic			Nonblastogenetic			Controls			<i>P</i>
	N	SA ^a	%	N	SA ^a	%	N	SA ^a	%	
With 2 pregnancies	568	65	11.44	5,546	664	11.54	6,629	657	9.91	0.001
With 3 or more pregnancies	644	253	39.29	5,466	2,073	37.93	5,389	1,986	36.85	0.32
Total	1,212	318	26.24	11,012	2,737	24.85	12,018	2,643	21.99	0.000002

^a Spontaneous abortions.

TABLE III. Number and Proportion of Pregnancies Ending in Spontaneous Abortion in Each Study Group

	Blastogenetic			Nonblastogenetic			Controls			<i>P</i>
	TP ^a	SA ^b	%	TP ^a	SA ^b	%	TP ^a	SA ^b	%	
Mother with only 2 pregnancies	1,136	65	5.72	11,092	664	5.99	13,258	657	4.96	0.002
Mother with 3 or more pregnancies	2,624	364	13.87	21,902	2,816	12.86	20,659	2,584	12.51	0.12
Total	3,760	429	11.41	32,994	3,480	10.55	33,917	3,241	9.56	0.00001

^a Total number of pregnancies.^b Spontaneous abortions.

preceding pregnancy is higher in mothers of infants with blastogenetic defects other than NTD than of those with NTD. The lowest proportion of spontaneous abortions was observed among mothers of infants with NTD. Comparing these proportions with those observed in controls (13.24%), as shown in Table V, the differences with the group of other blastogenetic defects and of nonblastogenetic defects are statistically significant ($P = 0.002$ and $P = 0.009$, respectively), whereas the difference with NTD is not ($P = 0.47$).

DISCUSSION

We have shown that mothers of infants with blastogenetic defects have a higher proportion of spontaneous abortions than mothers of control infants. These observations have led us to hypothesize that the increased incidence of spontaneous abortions may mask recurrence at birth.

We found that the proportion of mothers who had at least one previous abortion did not differ ($P = 0.29$) between mothers of infants with blastogenetic defects (26.24%) and mothers of infants with nonblastogenetic defects (24.85%). However, when we included the control group, the differences became statistically significant (0.000002). This suggests that mothers of malformed infants (of any type) have at least one previous abortion more frequently than mothers of control infants. Similar results were obtained when we analyzed the proportion of gestations ending in spontaneous abortion (Table III).

As shown in Table IV, in mothers with three or more gestations, the proportion of pregnancies ending in

spontaneous abortions was significantly higher ($P = 0.02$) in mothers of infants with blastogenetic defects other than NTD (14.85%) than in mothers of infants with nonblastogenetic defects (12.86). Similarly, the proportion of pregnancies that ended in spontaneous abortions in mothers of infants with blastogenetic defects other than NTD (14.85%) differed significantly from the proportion observed in mothers of control infants with three or more pregnancies (12.51%) (Table III). This suggests that blastogenetic defects other than NTD are highly lethal and increase the risk for spontaneous abortion, thus masking recurrence at birth. This also could be interpreted as that some women who have had spontaneous abortions are at a higher risk to have a child with blastogenetic malformations. In fact, the proportion of infants with blastogenetic defects among women who have had a spontaneous abortion at least (in those with 2 or more gestations), is 10.41%, whereas among women who have never had a known pregnancy loss (among those with one or more pregnancies) the proportion of infants with blastogenetic defects is 9.36 ($P = 0.067$). However, the proportion of infants with blastogenetic defects among women who have had spontaneous abortions among those with three or more gestations, is 10.88%, which differs significantly ($P = 0.02$) from the 9.36% observed in women without spontaneous abortions. Therefore, the low recurrence risk at birth at least for some of the blastogenetic defects may not necessarily imply that they are sporadic.

In contrast, the data in Table III also suggest a relationship between the occurrence of a spontaneous abortion in the preceding pregnancy and the birth of a child

TABLE IV. Number and Proportion of Pregnancies Ending in Spontaneous Abortion in Mothers of Infants With NTD, Other Blastogenetic Defects, and Nonblastogenetic Anomalies

	Blastogenetic									<i>P</i>
	NTD			Other blastogenetic			Nonblastogenetic			
	TP ^a	SA ^b	%	TP ^a	SA ^b	%	TP ^a	SA ^b	%	
Mother with only 2 pregnancies	452	28	6.19	684	37	5.41	11,092	664	5.99	0.081
Mother with 3 or more pregnancies	988	121	12.25	1,636	243	14.85	21,902	2,816	12.86	0.054
Total	1,440	149	10.35	2,320	280	12.07	32,994	3,480	10.55	0.07

^a Total number of pregnancies.^b Spontaneous abortions.

TABLE V. Number and Proportion of Mothers Who Had an Abortion Preceding Birth of an Infant With Blastogenetic Defects, Nonblastogenetic Defects, and Controls

	Blastogenetic	Nonblastogenetic	Controls	<i>P</i>
Number of mothers Preceding pregnancy was SA ^a :	1,212	11,012	12,018	
Number	196	1,675	1,591	
Proportion	16.17%	15.21%	13.24%	0.00002

^a Spontaneous abortion.

with malformations in mothers with only two pregnancies. As shown in Table IV, this was slightly higher for NTD than for other blastogenetic or nonblastogenetic defects, although the differences do not reach the level of significance. This difference disappeared when we pooled the group of mothers with only two pregnancies and those with three or more. Therefore, our data do not confirm the reported relationship between spontaneous abortions in the preceding pregnancy and NTD [Knox, 1970; Clarke et al., 1975; Carmi et al., 1994; Adám et al., 1995]. However, as previously noted [Gardiner et al., 1978], we identified a significantly higher proportion of spontaneous abortions preceding pregnancies resulting in infants with congenital defects (either blastogenetic other than NTD or nonblastogenetic) than those producing normal liveborn infants. But in contrast with previous observations, the occurrence of spontaneous abortions preceding the birth of an infant with NTD was not different from that of controls. It is conceivable that the differences between our results and those of other investigators may be due to differences in the genetic makeup of the populations rather than to environmental factors, such as the presence of trophoblastic remnants.

One should also consider the possibility of a recall bias in the ascertainment of previous spontaneous abortions in the control group. However, we consider this very unlikely since the interview of the mothers of cases and controls was done within the first 3 days after delivery. As we have observed previously, the data from the controls at this time are even more accurate than those from the cases [Martínez-Frías, 1993]. However, if a recall bias were present, it should also be observed in the analysis of NTD.

In summary, we have observed that in almost any group of mothers of malformed infants excluding NTD, the proportion of mothers with spontaneous abortions

or the proportion of gestations ending in abortion is statistically different from those observed in the mothers of normal liveborn (controls) infants. However, mothers of infants with blastogenetic defects have a higher number of previous spontaneous abortions than mothers of infants with nonblastogenetic defects. Thus, although it is true that, as Opitz [1993] stated, malformed infants with blastogenetic defects represent sporadic cases within a family, it is evident from our data that their mothers have more spontaneous abortions. This suggests the potential for an increased recurrence risk. Our results also suggest that the increased rate of abortions is not similar for all blastogenetic defects. As discussed above, it is not elevated in mothers of infants with NTD, whereas it is significantly higher in mother of infants with other blastogenetic defects than in mothers of infants with nonblastogenetic defects or normal controls. The analysis of the relationship between previous spontaneous abortions in mothers of infants with specific blastogenetic defects other than NTD could give us information on those of genetic cause.

In conclusion, the analysis of our data leads us to posit that mothers of most children with blastogenetic defects have a high proportion of abortions and, thus, a potentially increased risk of recurrence. This risk would reflect the influence of blastogenetic defects of genetic origin and of those caused by chronic exposure to teratogenic agents (such as maternal diabetes). From a practical standpoint, these factors should be suspected in mothers of infants with blastogenetic defects who have a history of previous spontaneous abortions.

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TABLE VI. Number and Proportion of Mothers Who Had an Abortion Preceding the Birth of an Infant With NTD, Other Blastogenetic Defects, and Nonblastogenetic Defects

	Blastogenetic		Nonblastogenetics	<i>P</i>
	NTD	Other blastogenetics		
Number of mothers Preceding pregnancy was SA ^a :	473	739	11,012	
Number	68	128	1,675	
Proportion	14.38%	17.32%	15.21%	0.26

^a Spontaneous abortions.

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